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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 05/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

AS

Office Action Summary	Application No.	Applicant(s)	
	09/994,143	CRAINE, BRIAN L.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment, Remarks and Declaration filed 04/06/04 are acknowledged. Claims 1-24 are pending in the application. Claims 25-29 are withdrawn from consideration.

Response to Amendment

2. Rejections of the pending claims remain the same as established in the previous Office action.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 5 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the location of GI bleeding when monitoring specific components of blood in a stool sample, i.e. heme proteins, by UV-Vis spectrometry, does not reasonably provide enablement for determining this location by monitoring any other components of the stool with any other absorption spectrometry (e.g. IR, NDIR, Raman, etc.). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification does not disclose any way for a person to define the source of bleeding when no specific wavelengths of the absorption spectra, UV-Vis in particular, or specific compounds, which should be monitored by these spectra, heme proteins in blood in particular, are known. Moreover, it is not even clear from the claims, which absorption spectra are recited in the claim, since the term "absorption spectra" is conventionally used in a context related to absorption and emission spectra, rather than in defining the wavelength range. There may be UV-Vis, IR, NDIR,

Raman, etc. absorption spectra. There is no way for anyone of ordinary skill in the art to determine the location of GI bleeding when monitoring unknown components of the stool by abstract "absorption spectra".

Claims 2-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the conditions recited in claim 13, does not reasonably provide enablement for other conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. It is well known from the extensive literature that the absorption lines of various haemoglobins and derivatives depend on pH of their solutions, and therefore while the peaks of hemoglobin are observed at 540 and 576 nm when pH 7.4, different absorption peaks will be observed for other pH values, see e.g. Ingberg et al. (US 5,008,388): "in the albumin, the absorption spectrum is again very similar to that of hemoglobin with a high Soret maximum at 402 nm and the maxima in the visible at 510, 540, and 620 nm, typical for a high-spin ferric hemoprotein. In aqueous alcohol, the intensity of the Soret band has decreased and the maximum has shifted to 393 nm, whereas the visible spectrum is more diffused with maxima at 490 and 602 nm. In 0.9% sodium chloride, the Soret maximum has decreased further and is shifted to 390 nm, while the spectrum in visible wave lengths shows only a broad band at 600 nm" (col. 6, lines 40-64).

5. Claims 23-24 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Specific IR wavelengths for detecting ferriheme and ferroheme in specific conditions critical or essential to the practice of the invention, but not included in the claim(s) are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). The specification does not disclose any possible IR wavelength range for detecting ferriheme and ferroheme, which may significantly vary depending on conditions.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. **Claims 1 and 5** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder et al. (US 5,460,969) with evidence of Benezra et al. (US 4,853,338) in view of Hacker (Arch. Verdauungs-Krankh., 1935, Abstract).

Fielder teaches a method for differentiating between locations of GI bleeding (upper or lower) based on detection of hemoglobin in a filtered and centrifuged stool sample, with the presence of hemoglobin indicating lower location of GI bleeding (Abstract), while "detection of hematin [a **ferric** heme derivative (Merck Index, 9th edition, see Benezra, col. 5, lines 56-57), with hemoglobin being **ferro**heme] in the stool will signify upper GI blood loss" (col. 2, ll.1-2). "In the present invention, a liquid stool sample is prepared in which fecal material is dispersed in solution to dissolve any hematin and hemoglobin present in the stool sample. Hematin is preferentially precipitated and separated from the solution. The remaining solution is subjected to a diagnostic assay for peroxidase activity. Since hemoglobin which has passed through the

stomach and upper gastrointestinal tract will have been substantially converted to hematin by stomach acid, the presence of peroxidase activity in the separated solution is an indication of the presence of hemoglobin only, which has originated in the lower gastrointestinal tract" (col. 2, lines 35-52).

Fielder does not specifically disclose spectroscopic measurement of the samples.

Hacker teaches "detection of occult bleeding in the gastrointestinal tract with special reference to the appearance of copratoporphyrin and hemoglobin" (Title), comprising spectroscopic examination of hemoglobin degradation products in feces, such as hematin and "copratoporphyrin".

It would have been obvious for anyone of ordinary skill in the art to apply spectroscopic approach taught by Hacker in Fielder's method of differentiating between locations of GI bleeding, because both Fielder and Hacker consider presence of unchanged hemoglobin (ferrous heme) in a stool sample as an indication of lower GI bleeding and the presence of hematin (ferric heme) as a sign for upper GI bleeding, with spectrometric approach being simpler and more straightforward. It would have been obvious for anyone of ordinary skill to use a reference sample without the stool sample for calibrating spectrometer and correcting for the background noise, because this is a conventional way of calibrating spectrometers with a blank sample.

10. **Claims 2-4 and 6-8** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker, as applied to claim 1 above, and further in view of Brady et al. (JBC, 1975).

Fielder and Hacker in the Abstract do not specifically teach absorption peaks at 540 nm, 576 nm, 415 nm and 408 nm.

Brady discloses ferroheme and ferriheme spectroscopic parameters with absorption of ferroheme at 415 nm, 540 nm and 570 nm, and Soret absorbance of ferriheme at 407 nm.

It would have been obvious for anyone of ordinary skill in the art to detect the presence or absence of peaks at 540 nm, 576 nm and 415 nm, and for Soret line at 407-408 nm, disclosed by Brady, in Fielder-Hacker method, because the first set of absorptions is characteristic for hemoglobin, while Soret line at 408-409 nm is characteristic for hematin.

11. **Claims 9, 14-15 and 20-21** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker and Machida et al. (US 5,759,866).

Fielder teaches a method for differentiating between locations of GI bleeding (upper or lower) based on detection of hemoglobin in a filtered and centrifuged stool sample, with the presence of hemoglobin indicating lower location of GI bleeding (Abstract), while "detection of hematin [a **ferric** heme derivative (Merck Index, 9th edition, see Benezra, col. 5, lines 56-57), with hemoglobin being **ferro**heme] in the stool will signify upper GI blood loss" (col. 2, ll.1-2).

Fielder does not specifically disclose spectroscopic measurement of the samples.

Hacker teaches "detection of occult bleeding in the gastrointestinal tract with special reference to the appearance of copratoporphyrin and hemoglobin" (Title), comprising spectroscopic examination of hemoglobin degradation products in feces, such as hematin and "copratoporphyrin".

Fielder and Hacker do not particularly disclose nitrocellulose filter.

Machida indicates in the "Background of the Invention" a conventional use of nitrocellulose filter for the examination of fecal occult blood" (col. 1, lines 41-45).

It would have been obvious for anyone of ordinary skill in the art to apply spectroscopic approach taught by Hacker in Fielder's method of differentiating between locations of GI bleeding, because both Fielder and Hacker consider presence of unchanged hemoglobin (ferrous heme) in a stool sample as an indication of lower GI bleeding and the presence of hematin (ferric heme) as a sign for upper GI bleeding, with spectrometric approach being simpler and more straightforward. It would have been obvious for anyone of ordinary skill to use a reference sample without the stool sample for calibrating spectrometer and correcting for the background noise. It would have been obvious to use nitrocellulose filter, because Machida indicates its conventional usage for analysis of biological samples. It would have been obvious to use either fecal extracts or deposit on the filter for spectrometric analysis, because both ways are conventional for this type of analysis and purify the samples using conventional biochemical separation methods.

12. **Claims 10-12 and 22** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker and Machida, as applied to claims 9, 14-15 and 20-21 above, and further in view of Brady et al. (JBC, 1975).

Fielder in view of Hacker and Machida do not specifically teach absorption peaks at 540 nm, 576 nm, 415 nm and 408 nm.

Brady discloses ferroheme and ferriheme spectroscopic parameters with absorption of ferroheme at 415 nm, 540 nm and 570 nm, and Soret absorbance of ferriheme at 407 nm.

It would have been obvious for anyone of ordinary skill in the art to detect the presence or absence of peaks at 540 nm, 576 nm and 415 nm, and for Soret line at 407-408 nm, disclosed by Brady, in Fielder-Hacker-Machida's method, because the first set of absorptions is characteristic for hemoglobin, while Soret line at 408-409 nm is characteristic for hematin.

13. **Claim 13** is rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker and Machida, as applied to claims 9, 14-15 and 20-21 above, and further in view of Schmitz (US 4,347,311).

Fielder, Benezra, Hacker and Machida do not disclose TE-buffer recited in claim 13; however Benezra teaches detecting hemoglobin at 540 nm and 576 nm in phosphate buffer at pH 7.5.

Schmitz discloses TE-buffer recited in claim 13 with pH 7.4 used for separating biological samples.

It would have been obvious to use TE-buffer with pH 7.4, disclosed by Schmitz for extracting biological samples, in Fielder-Hacker-Brady-Machida's method, because Benezra teaches detecting hemoglobin at pH 7.4 as the closest biological conditions.

14. **Claim 16** is rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker and Machida, as applied to claims 9, 14-15 and 20-21 above, and further in view of HYDROFLUOR^{TM}-Combo.

While Fielder in view of Hacker and Machida do not particularly disclose applying glycerol to the filter, HYDROFLUOR^{TM}-Combo discloses applying glycerol to the cellulose filter to make it transparent for the spectroscopic studies of the biological sample on the filter. It would have been obvious for anyone of ordinary skill in the art to apply glycerol to the nitrocellulose filter for the same reasons as indicated in HYDROFLUOR^{TM}-Combo, i.e. to make it transparent for spectrometric analysis.

15. **Claims 16-19** are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielder with evidence of Benezra in view of Hacker and Machida, as applied to claims 9,14-15 and 20-21 above, and further in view of "Manual for Biochem 651" and well-known mathematical algorithms for treating complex spectra.

Fielder, Benezra, Hacker and Machida do not specifically disclose the ways of treating complex absorption spectra of heme-derivatives in different states using various mathematical algorithms.

Manual for Biochem 651 provide a simplified approach for treating such spectra for complex mixtures of heme in different states. It would have been obvious for anyone of ordinary skill in the art to apply well-known mathematical algorithms to treating complex absorption spectra of hemoglobin in different states, similar to what is provided in the Manual, using more sophisticated mathematical models, such as neural network, Simplex, or Gaussian Jordan elimination algorithm, because such models are well-known for using in treating complex absorption spectra, as admitted by the Applicants (Specification, page 20, lines 10-13).

Response to Arguments

16. Applicant's arguments filed 04/06/04 have been fully considered but they are not persuasive. The Applicant's arguments regarding rejections of claims 1, 5 and 9 under 35 U.S.C. 112, first paragraph, related to the scope of enablement, which are based on the Inventor's Declaration, in fact support the position of the examiner. The Remarks state: "as explained in paragraph 6 of the Craine's Declaration, a person skilled in this art wanting to perform the method of the claimed invention in accordance with the description provided in the specification would ordinarily have a prepared reference samples having the same pH as the stool test sample and used the spectrophotometer to determine the peak values of the main Soret band and also to determine any visible additional absorption peaks of both pure hemoglobin (ferrous heme) and acid-treated hemoglobin (ferric heme) before using the same spectrophotometer to determine the values of corresponding peaks in the spectrum of the stool test sample". That is, a person of an ordinary skill in the art should know, which compounds in a stool sample containing blood, i.e. ferrous heme and ferric heme, should be monitored, and at which specifically wavelengths (Soret band in UV-Vis spectra) in order to practice the invention. The examiner indicated exactly that; a person of ordinary skill in the art can practice the invention in the scope disclosed in the specification, but not in the scope of the claims, which recite "a method for determining whether blood in a stool came from an upper gastrointestinal

site or a lower gastrointestinal site, comprising the steps of: (a) collecting a stool sample and preparing it for analysis by spectroscopy; (b) determining a sample absorption spectra of the stool sample; and (c) determining whether the blood in the stool came from the upper gastrointestinal site or the lower gastrointestinal site based on an analysis of the sample absorption spectra". How is anyone of ordinary skill in the art can practice the invention in the scope of these claims? Which of numerous stool components should be monitored? By what type of absorption spectrometry? Raman, IR, NDIR, UV, etc.? There is no way any routineer in the art can practice the invention in the scope of these claims. The issue aroused was not related to the preparation of the reference sample, but rather to defining, which specifically compounds in the stool sample and by which particularly absorption spectroscopy should be monitored for determining the GI bleeding location.

Arguments regarding rejections of claims 2-12 under 35 U.S.C. 112, first paragraph, also support the examiner's position. As the Applicant indicated, and as can be concluded from the Table provided in the Declaration, pH range is in fact essential for discerning between ferrous and ferric hemes. Specifically, at pH 4.5 absorption band positions in UV-Vis spectra become very close for both types of hemoglobins, which makes the method un-enabled. These data confirm that the signal positions do not change in a quite narrow pH range of 6.8-8.0, close to neutral pH 7. Since such pH range is the only one, which makes the method enabled, it should be reflected in the claims. pH values outside this range make the method un-enabled. While the examiner was not aware of the Applicant's data, they appear to confirm the grounds for rejection of claims 2-12 under 35 U.S.C. 112, first paragraph.

As for rejections of claims 23 and 24: the specification discloses the method for determining locations of GI bleeding based on the presence or shift of Soret band (UV-Vis region of absorption spectra) for ferrous and ferric hemes. It does not disclose any possible IR parameters of these proteins. Moreover, dependent claims 23 and 24 do not even recite ferrous and ferric hemes. There is no way for a person of ordinary skill in the art to measure IR spectra of stool samples in the range from about 2 μm to 2000 nm (IR range) and then define, where GI bleeding is coming from.

Regarding the rejection of the pending claims over the prior art. While the Remarks and Declaration are quite convincing in respect to differences between the disclosed method and the

prior art, the subject matter of the pending claims still read on the prior art. The pending claims do not reflect any particulars of the method described in the Remarks and Declaration. The claims the way they are written appear to recite monitoring of modified and unmodified heme proteins by absorption spectra, with modification occurred under stomach acidic conditions. This allows determining the location of GI bleeding, especially since Fielder specifically indicates that the presence of hematin indicates upper GI bleeding and the presence of hemoglobin – lower GI bleeding. The claims do not reflect any monitoring of different ferric hemes besides hematin; they read on the prior art of Fielder in view of Hacker not because Hacker discloses determining the location of GI bleeding, but rather because he demonstrates convenience of using spectrometric method for detecting degradation products of hemoglobin, with hemoglobin having a characteristic Soret band in UV spectrum, and because Fielder indicates the way to determine GI location by detecting hemoglobin or products of its degradation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
5/20/04